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主持人 ：林本元　台北醫學院藥學研究所

一、中文摘要 ：

斑蝥素胺由斑蝥要與一級氨在約 200°反應所得，探討天然斑蝥胺(Cantharidinimides)在天然物化學中，具簡單且非常特別的分子結構，在基礎化學與藥物研究開發上極具潛力的標的物。在文獻中記載之藥理活性中具除了具抗癌作用外，在經化學修飾發現抑制 Xanthine oxidase 得藥理活性，並發現具有冠狀動脈舒張的作用。本計畫進行斑蝥素胺合成，經由三環的 activated aziridines 的開環作用，產生 amide 或 amine 的衍生物。

關鍵字 ：斑蝥素，斑蝥素胺，Actived aziridines

Abstract :

Cantharidine was converted to cantharidinimides by reaction with primary amines at ca. 200°C. Products with a slightly modified basic structure have also been synthesized in an analogous manner. Several of them showed anticonvulsant and antixanthine-oxidase activities. Cantharidinimides with N-substituents seem to be unknown at present, although they may potentially exhibit more than antitumor activities. This projects showed that another cantherinimides were synthesized via ring opening of activated aziridines, and might obtain some new cantharidinimides and these bioactivities were tested.

Keywords : Cantharidin, cantharidinimides, activated aziridines.

二、緣由與目的 ：

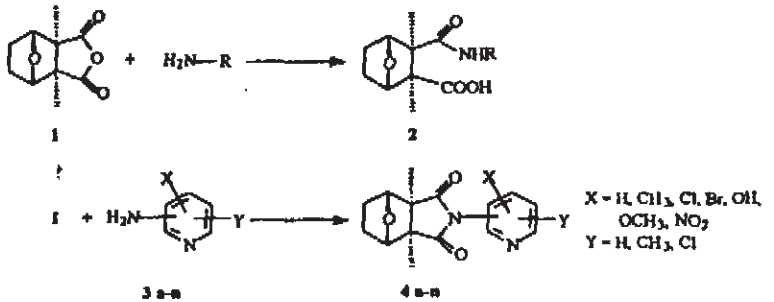
據文獻，斑蝥素極具毒性，觸及皮膚造成潰爛及發泡，並不適於醫學上的治療，但若加以修飾，即將酸酐的部份做成斑蝥素胺，則除了具有擴張血管作用外，近幾年來也有報導具抗肝癌的作用。本計畫將斑蝥素胺經由打開 activated aziridines 的環以合成不同類型的斑蝥素胺，並測驗其藥理活性。在本系列中，我們也利用 aminopyridines 及其衍生物來合成斑蝥素胺，由 aminopyridine 和 aminoaniline 之衍生物中，pKa 值的差異乃至影響反應生成率，也作論文並發表論文。希望此系列的合成，能運用在合成其他藥物，上，找出更好的方法及更有效，毒性低之化合物。

PRESSURE SYNTHESIS OF NOVEL N-PYRIDYLCANTHARIDINIMIDES

Synth. Commun. **1999**, *29*, 1611

Pen-Yuan Lin*, Sheng-Jie Shi, Lun-Huei Lin and Feng-Lin Hsu*
School of Pharmacy, Taipei Medical College, Taipei City Wu-Shing St. 250, Taiwan

The present investigation extended the improved synthesis in order to obtain a novel type of cantharidinimides in usable yields and to simultaneously study the scope of this synthesis.

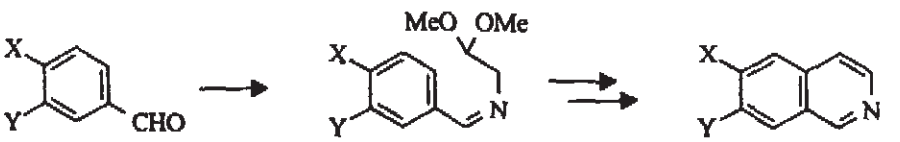


IMPROVED PROCEDURES FOR LARGE SCALE PREPARATION OF 6- AND 7-OXY-SUBSTITUTED ISOQUINOLINES AND A CONVENIENT WORK-UP PROTOCOL FOR TITANIUM SUPPORTED REACTIONS.

Synth. Commun. **1999**, *29*, 1617

Ralf Kucznierz*, Joachim Dickhaut, Herbert Leinert and Wolfgang von der Saal, Chemical Research Department, Boehringer Mannheim GmbH, D-68298 Mannheim, Germany

Improved Pomeranz-Fritsch type procedures for large scale preparation of 7-methoxy-isoquinoline (3a), isoquinolin-7-ol (3b), 7-methoxy-isoquinolin-6-ol (3c) and 6-methoxy-isoquinoline (7) are reported.



3a (Y=OMe, X=H)
3b (Y=OH, X=H)
3c (Y=OMe, X=OH)
7 (Y=H, X=OMe)

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Synthesis of Cantharidinimide Derivatives via the Mitsunobu Reaction

*Pen-Yuan Lin**
Sheng-Jie Shi
*Feng-Lin Hsu**
School of Pharmacy,
Taipei Medical College,
Taipei 110-31, Taiwan, R.O.C.

Key Words
Cantharidin
Cantharidinimide
Mitsunobu reaction

ABSTRACT
Derivatives of cantharidinimide compounds **4a-c** were synthesized from reactant **2** and **3a-c** in dry tetrahydrofuran with triphenylphosphin and diisopropylazodicarboxylate, using a novel application of the Mitsunobu reaction.

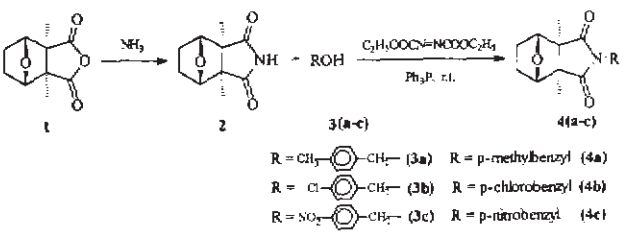
INTRODUCTION

Cantharidin (1), a strong acantholytic, is isolated from the family Molodae.[1] It is reported to have extremely high potency[2] and shows toxic properties which make it an antineoplastic agent. Its potential bioactivity has stimulated research on cantharidinimides and related imides. Several modifications of cantharidinimide compound **2** have been made to reduce toxicity and promote bioactivity. N-methylcantharidinimide compounds have shown an inhibitory action on tumors in animals.[3] These compounds were synthesized from cantharidin and amines in triethylamine by heating to 200 °C. Walker used the Mitsunobu reaction to successfully synthesize N-alkylmaleimides.[4] This procedure also allows the direct formation of N-alkylcantharidinimide as shown in Scheme 1. It is a more general procedure since it can be carried out under anhydrous conditions and at room temperature or with reflux. A review of the literature revealed that these conditions have not been used before to synthesize N-arylcantharidinimide.

RESULTS AND DISCUSSION

As shown in Table 1, compound **2** is well suited as a nucleophile in this reaction and was successfully condensed with p-chlorobenzyl alcohol **3b** in a variety of conditions, providing **4b** in a 18%-62% yield. The study was then extended to a series of alcohols, the results of which are summarized in Table 2. By using the same method at room temperature, we treated p-methylbenzyl alcohol **3a** and p-nitrobenzyl alcohol **3c** with 2 in THF and successfully obtained **4a** in a yield of 70% and **4c** at 48%, respectively. We assumed that the methyl and halogen groups might exhibit an activating effect on the benzene ring and the methyl, chloro, and nitro functional groups might exert an inductive effect with their acidity influencing the reaction. As shown in Table 2, **4a** has the highest yield, followed by **4b**, and then **4c**. Our results indicate that the electron-withdrawing capabilities at the meta and

Scheme 1



NTJM
Tel: 886-2-27361661 ext. 749
Fax: 886-2-23772150

Dr. Pen-Yuan Lin
School of Pharmacy, Taipei Medical College,
250, Wu Shing Street, Taipei 110-31, Taiwan, R.O.C.
Tel: 886-2-27361661 ext. 672
E-mail: LPY0620@tmc.edu.tw

Table 1. Conditions of the Mitsunobu Reaction for the Synthesis of (4b)

Entry	Condition		Ratio[a]	Yield (%)[b]
	Reflux (12 h)	RT (12 h)		
1	+	-	1:1:1:1	18
2	-	+	1:1:2:2	24
3	-	+	1:1:1.5:1.5	46
4	-	+	1:1.2:1.5:1.5	62

[a] Molar ratio of compound **2**: p-chlorobenzyl alcohol: diisopropylazodicarboxylate: triphenylphosphin.

[b] Obtained after purification by chromatography on silica gel.

ortho positions on the benzene ring were low. In contrast, the electron-donating group had a good yield, particularly at the para position on the benzene ring.[5]

EXPERIMENTAL SECTION

Instruments

Infrared spectra were recorded on a Perkin-Elmer Model 882 (New York, U.S.A.) and a Nicolet 510 PFT (New York, U.S.A.) spectrophotometer. Proton NMR spectra were obtained on a Bruker AC-300 and a Bruker DRX-500 (Karlsruhe, Germany). Melting points were determined using a Yanaco MP-S3 (Tokyo, Japan) melting point apparatus. Mass spectra were obtained on a Joel JMS HX 110 FABMS (Tokyo, Japan) spectrometer.

General Procedures

The reaction of compound **2** with alcohols (**3a-3c**): Alcohol was added to distilled tetrahydrofuran (20 mL), and then triphenylphosphin (0.4 mM) and compound **2** (0.3 mM) were added. After 10 min diisopropyl azodicarboxylate (0.4 mM) was added and the reaction was stirred for 12 h under N_2. After the solvent was removed under reduced pressure and the resulting residue was triturated with 1:1 hexane/Et_2O to remove the Ph_3PO by-product, the crude product was purified by SiO_2 chromatography. The residue was crystallized from MeOH.

N-4-methylbenzylcanthaidinimide (4a)

Mp 120-122 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.10 (6H, s, CH_3 × 2), 1.66-1.77 (4H, m), 2.27 (3H, s, C4-CH_3), 4.55 (2H, s, OCH), 4.59 (2H, s, NCH_2), 7.06 (2H, d, J = 7.5 Hz, phenyl H-3, H-5), 7.16 (2H, d, J = 7.5 Hz, phenyl H-2, H-6); IR (KBr): 1734 cm^{-1} (amide); MS *m/z* (rel. int): 299 $[M]^+$ (30), 105 (100), 138 (60).

Table 2. Preparation of Cantharidinimides 4a-c

Entry	Substrate	Product	Yield (%)[a]
1	**3a**	**4a**	70
2	**3b**	**4b**	62
3	**3c**	**4c**	48

[a] Obtained after purification by chromatography on silica gel.

N-4-chlorobenzylcantharidinimide (4b)

Mp 124-125 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.11 (6H, s, CH_3 × 2), 1.68-1.79 (4H, m, CH_2 × 2), 4.56 (2H, s, OCH), 4.60 (2H, s, NCH_2), 7.45 (2H d, J = 6.8 Hz, phenyl H-2, H-6), 7.65 (2H, d, J = 6.8 Hz, phenyl H-3, H-5); IR (KBr), 1700 cm^{-1} (amide); MS *m/z* (rel. int): 319 $[M]^+$ (20), 138 (40), 125 (50), 70 (100).

N-4-nitrobenzyl-cantharidinimide (4c)

Mp 168-169 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.11 (6H, s, CH_3 × 2), 1.66-1.77 (4H, m, CH_2 × 2), 227 (3H, s, CCH_3), 4.55 (2H, d, J = 2.2 Hz, OCH), 4.59 (2H, s, NCH_2), 7.44 (2H, d, J = 8.5 Hz, phenyl H-2, H-6), 8.14 (2H, d, J = 8.6, phenyl H-3, H-5); IR (KBr): 1733 cm^{-1} (amide); MS *m/z* (rel. int): 330 $[M]^+$ (5), 85 (30), 71 (70), 57 (100).

ACKNOWLEDGEMENTS

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